# INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

February 2020

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NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2020

# INA-RESPOND newsletter

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# content

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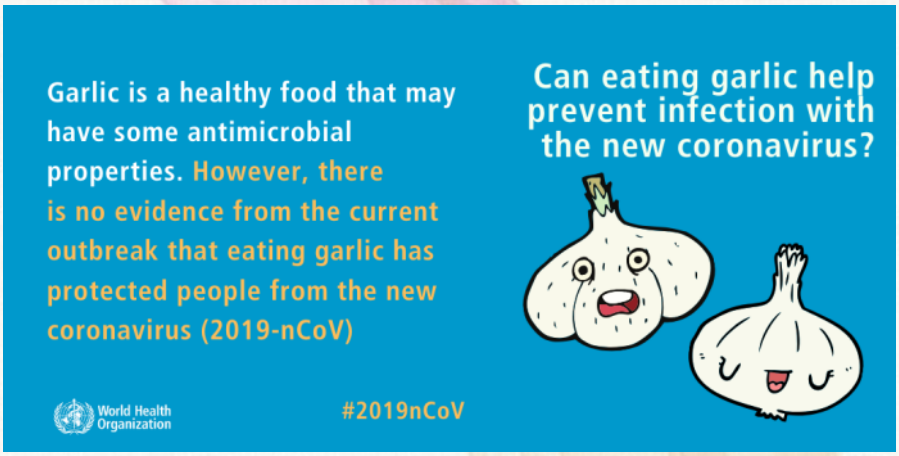
## FEATURES

INA-RESPOND Newsletter

# FEAR DRIVEN PUBLIC AWARENESS (AND PANIC?)

By: Aly Diana




An outbreak of novel coronavirus (2019-nCoV) that began in Wuhan, China, has spread rapidly, with cases now confirmed in multiple countries. This current outbreak of coronavirus infection is a threat to the health of the public and lead to a breaking news story that changes hour by hour. WHO has published a daily situation report since January 21, showing numbers of newly reported cases and numbers of confirmed, severe, and death cases globally and in China. Started with 282 confirmed cases from four countries, the number of cases has grown to 40,554 confirmed cases from 25 countries in 21 days (as per 11 Feb 2020). Given the incubation period of 14 days, hopefully, the number will start to plummet soon enough. Fingers crossed.

In the case of 2019-nCov, countries, international agencies, media, and people, in general, have contributed in one way and another to create awareness and somehow panic around the world. A lot of information has been released from credible and not so credible sources, performing both helpful and damaging effects. WHO has tried to counter some of the false beliefs in public and has created the Myth Busters section on its website and provided free online courses. CDC has also published guidance for public and healthcare professionals. The New England Journal of Medicine has dedicated a special webpage for 2019-nCov, inviting scientists to submit their novel findings and promise to publish with a speedy process and make the articles open access. The growth of published papers (and their citations) on 2019-nCov is remarkable. The paper which published the genome sequenced of 2019-nCov is probably the most cited paper in history over a very short period (40 citations in 20 days – published on January 24, 2020). It is interesting to see how the world reacts to 2019-nCov, and to observe a wide range of different reactions. I am waiting for a 'somewhat success story' on how people interact together to fight 2019-nCov; and how much we can learn from what happened.

My two cents: Indeed, the 2019-nCov is scary. However, other scary diseases should not just slide away into the dark, only because they have not caused global fear and flown under the media's radar. For example, tuberculosis infected an estimated 10.0 million and killed 1.24 million HIV-negative people in 2018, and the latest anti-TB drug resistance surveillance data show that 3.5% of new and 18% of previously treated TB cases in the world are estimated to have multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB). In 2017, an estimated 558 000 new cases of MDR/RR-TB emerged globally and caused 230,000 deaths in 2017. From 550,000 estimated new cases, only 161.000 detected, and only 139.000 started treatment (with only 55% treatment success, 15% died, 8% treatment failed, and 21% were lost to follow-up/not evaluated). In brief, the number of people enrolled in treatment was equivalent to only one in three of the approximately half a million people who developed MDR/RR-TB; and two-thirds were roamed free and infected other people with drug-resistant bacteria. Do we wear a mask to protect ourselves from tuberculosis? Do we care? Do we have enough fear to start the same awareness?

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INA-RESPOND Newsletter

# TRIPOD & INA-PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Maria Intan Josi, M. Ikhsan Jufri, Venty Muliana Sari

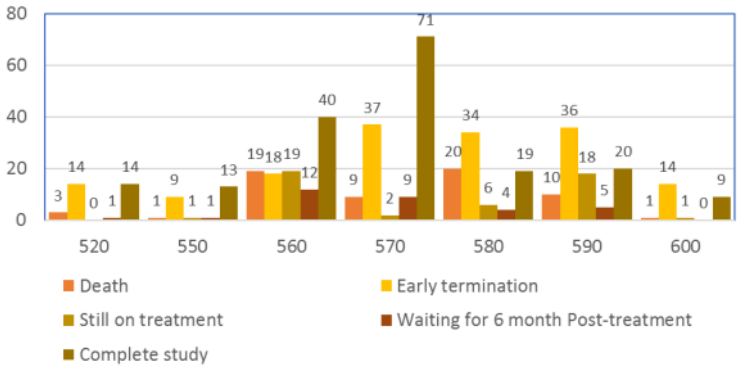



*Figure 1.Participant status per site based on uploaded CRF per 5 Feb 2020*

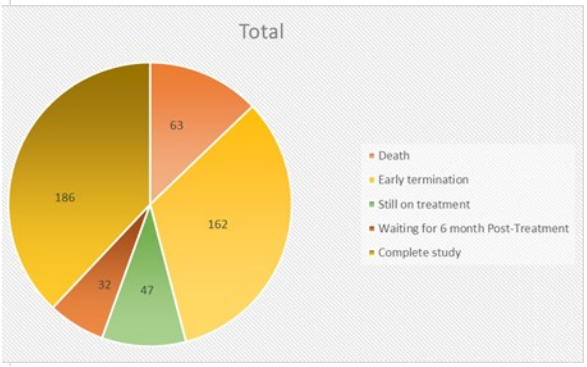



*Figure 2. Total Participants Status based on uploaded CRF per 5 Feb 2020*

STUDY UPDATES

## INA102

### PARTICIPANT STATUS

Per 5 Feb 2020, the total ongoing participants in TRIPOD study are 79 out of 490 enrolled participants. From those 79 ongoing participants, 47 are still on TB treatment while 32 are waiting for their 6-month post-treatment visit. One hundred eighty-six participants have completed the study while 225 participants are terminated early (including death). Therefore, there are still 16.1 % participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, there are 1 participant from site 520 (RS Sanglah Denpasar) who still need to be followed up, 2 participants from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar), 31 participants from site 560 (RSUP dr. Kariadi Semarang), 11 participants from site 570 (RSUD dr. Soetomo Surabaya), 10 participants from site 580 (RSUP dr. Sardjito Jogjakarta), 23 participants from site 590 (RSUP Persahabatan Jakarta), and 1 participant from site 600 (RSUP dr. Adam Malik Medan).

### AWAITING CULTURE AND DST RESULT

All culture result and Drug Sensitivity (DST) result from all sites has been completed. There are 932 isolate sputum culture are collected. A plan for re-testing isolate sputum culture will be discussed in near future. Re-testing for some of isolate sputum culture will be performed to seek a confirmatory result as additional data for available results. Material Transfer Agreement (MTA) will be one of the steps that need to be taken for sample re-testing since sample will be assessed abroad. MTA submission still on preparation progress. Sequentially, the sample shipment will be processed after MTA's approval obtained.

| Site number | Site name | Author |
|---|---|---|
| 520 | RS Sanglah Denpasar | dr. I Gede Ketut Sajinadiyasa, Sp.PD |
| 550 | RSUP dr. Wahidin Sudirohusodo | Dr. dr. Irawaty Djaharuddin, SpP(K) |
| 560 | RSUP dr. Kariadi | dr. Banteng Hanang Wibisono, Sp.PD-KP |
| 570 | RSUD dr. Soetomo | dr. Tutik Kusmiati, SpP (K) |
| 580 | RSUP dr. Sardjito | dr Bambang Sigit Riyanto, SpPD-KP, FINASIM |
| 590 | RSUP Persahabatan | dr. Diah Handayani, SpP |
| 600 | RSUP H Adam Malik | Dr. dr. Bintang YM Sinaga, M.Ked(Paru), Sp.P(K) |

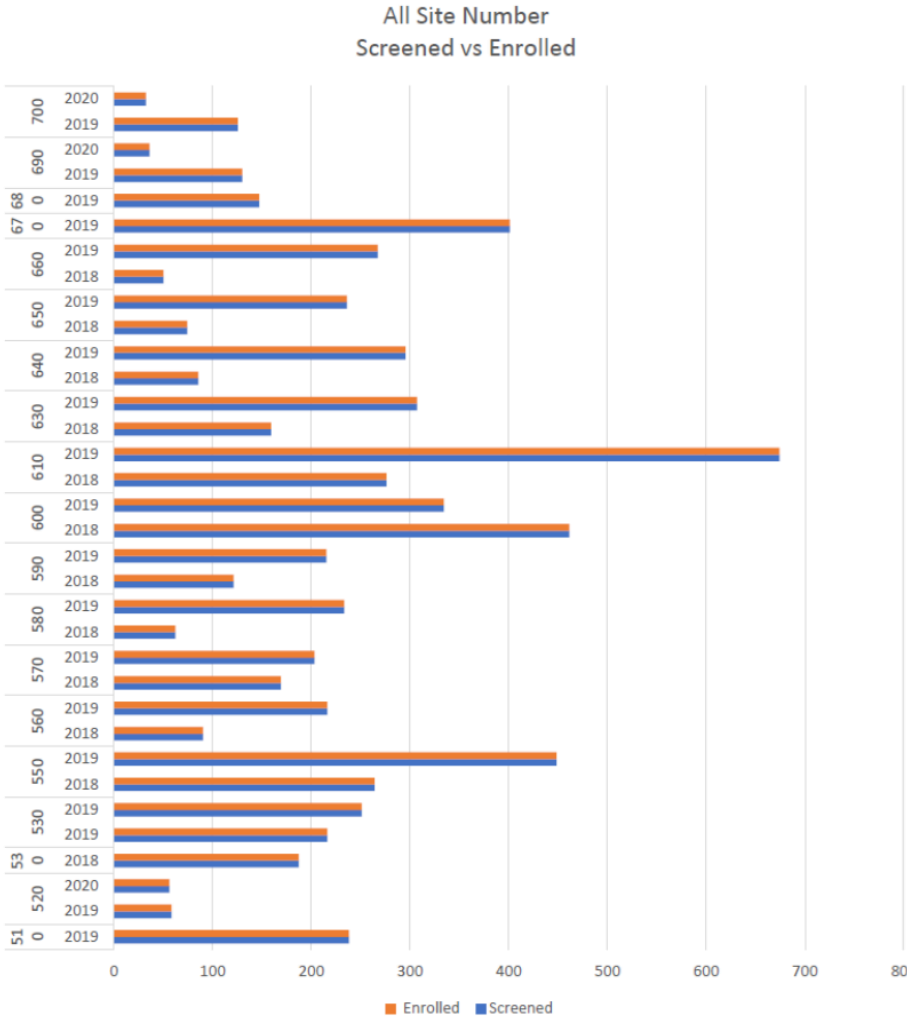
*Table 1. Author List of TRIPOD Manuscript*

## INA104

Three INA-PROACTIVE sites are still conducting screening and enrollment of new subjects. These sites are going to continue their screening and enrollment until 30 June 2020. Site 700 (T.C. Hillers Hospital in Maumere) and Site 690 (Abepura Hospital in Papua) have targeted to enroll five subjects per week, and site 520 (Sanglah Hospital in Bali) expects to enroll up to 8 subjects per week. The other 16 sites have ended their enrollment and are focusing on performing follow-up visits.

By 2 February 2020, 19 study sites had enrolled 4,172 subjects from 7,116 screened subjects. The total enrollment consists of 3,986 adults and 186 pediatrics. Numbers of screened and enrolled subject from each site are shown in figure 1 on the right.

From a total of 4,172 enrolled subjects, there are 96 end-of-study subjects due to death, withdrawn consent, and moving away. Details of end-of-study distribution per site are shown in Figure 2.




The Statistical Analysis Plan (SAP) meeting to discuss current data and the analysis plan for the INA-PROACTIVE study was conducted on 23-24 January 2020. Core-Protocol Team, NIAID, Kirby, and INA104 Secretariat Team attended the meeting. On the first day, participants discussed protocol secondary objective and current data situation. On the second day, they decided which data will be included in the INA104 main paper and discussed how the data will be analyzed statistically. From the SAP meeting, the INA104 team has some homework to support sites that did not perform data entry as expected. Therefore, the Secretariat team needs to conduct several strategic site managements to resolve their data issues. This month, the Secretariat team which consists of the Chair of INA-RESPOND, Site Specialists, and Data Management will perform site Interim Monitoring Visit to site 550 – Wahidin Sudirohusodo, Makassar, site 570 – dr Soetomo Hospital, Surabaya, site 540 – RSPI Prof dr Sulianti Saroso, and site 590 – Persahabatan Hospital, Jakarta in March 2020. Other study sites will be supported by regular TC or frequent communication via email.

| Site Number | Subject | | Total End of Study | Total Existing Subject |
|---|---|---|---|---|
| | Total Screened | Total Enrolled | | |
| 510 | 238 | 208 | 0 | 208 |
| 520 | 114 | 58 | 0 | 58 |
| 530 | 403 | 310 | 9 | 301 |
| 540 | 251 | 182 | 0 | 182 |
| 550 | 712 | 337 | 14 | 323 |
| 560 | 306 | 230 | 8 | 222 |
| 570 | 372 | 313 | 5 | 308 |
| 580 | 295 | 220 | 0 | 220 |
| 590 | 336 | 249 | 19 | 230 |
| 600 | 795 | 338 | 13 | 325 |
| 610 | 950 | 327 | 13 | 314 |
| 630 | 466 | 245 | 2 | 243 |
| 640 | 380 | 225 | 0 | 225 |
| 650 | 310 | 229 | 5 | 224 |
| 660 | 317 | 222 | 1 | 221 |
| 670 | 401 | 126 | 3 | 123 |
| 680 | 147 | 115 | 0 | 115 |
| 690 | 166 | 105 | 2 | 103 |
| 700 | 157 | 133 | 2 | 131 |
| Grand Total | 7116 | 4172 | 96 | 4076 |

Figure 2. Total end of study and existing subject

INA-RESPOND Newsletter

# 2020 THE ANNUAL BIOMEDICAL EXPLORATION WORKSHOP

By: M. Ikhsan Jufri


REPORT

I had a chance to participate in *2020 The Annual Biomedical Exploration Workshop* from 2 to 15 January 2020, which took place at Taipei Medical University (TMU), TMU Research Core Centre, TMU Interdisciplinary College, TMU Hospital, and Shuang Ho Hospital, Taiwan. This event was organized by the Master/Ph.D. International Graduate Programme in Medicine (IGPM) of Taipei Medical University and supported by the Ministry of Education (MOE) of Taiwan. The courses are designed for young scientists, junior principal investigators (PIs), and project executors to accelerate their transition to multiple talented scientists, research -independent PIs, and experienced project managers. In the long run, after the completion of the workshop, all registered trainees are hoped to become valued members in their profession and be willing to promote the regional cooperation in medical education and biomedical research among countries like Taiwan, Vietnam, Indonesia, and Malaysia, leading to the acceleration of biomedical industry developments in the future.

The workshop was attended by a total of 58 listed participants, including more or less 25 travel grantees, self-funded participants, and IGPM students. Participants' composition is students, scholars, or professionals from Vietnam, Indonesia, and Malaysia with multidisciplinary health professions: Medical doctors, Immunologists, Biologists, Pharmacists, Nurses, Public Health, and TMU's Students who wanted to join the class related to their research.

This workshop provided trainees with multidiscipline courses including methodology applied in clinical trials and cancer research; the updated knowledge in molecular and cell biology to un-braid the molecular pathogenesis of diseases; animal models for the study of human disease and drug discovery; bioinformatics; research and publication ethics; and technology authorization and transfer. These fundamental courses are intended to help participants convert bench studies to publications, useful clinical practices, and therapeutic agents or applications. Also, the workshop offered field trips to TMU experimental research core center,

the university-affiliated hospitals, and sightseeing tours during the program. In addition to these comprehensive courses, all trainees also experienced TMU achievements and traditional Taiwanese culture during this 14-day workshop.

My participation in 2020 The Annual Biomedical Exploration Workshop is a part of the INA-RESPOND network's program in providing continuous improvement for its employees. For years, INA-RESPOND commits on providing human capacity building for Indonesia in the field of clinical research not only for network hospitals but also for the secretariat team members. The INA-RESPOND aims to conduct basic and clinical research, increase the understanding of the pathogenesis of diseases, and prevent and treat infectious diseases based on the concerns of the country and in alignment with the priorities of the Indonesian Ministry of Health. It is intended that the research conducted by this network will aid in the development of public health policies and build sustainable research capacity in Indonesia.

The aims of this workshop were in line with INA-RESPOND objectives. During the workshop, I was able to gain more knowledge and experiences to understand research better in comprehensive ways and perspectives. Briefly, from this scientific event, we learned many things related to biomedical research from A to Z, including but not limited to:

1. How to make an idea for research (backgrounds and study problems);
2. How to do the research itself (methodology);
3. How to handle ethical issues (IRB);
4. How to use it for medical purposes (Application/ Translational medicine);
5. How to protect our rights on the invention (patent).

This workshop provided participants with not only a better understanding and insight from the courses but also an excellent opportunity to broaden their knowledge and enrich their experiences. Meanwhile, the participant was able to do networking and to experience collaboration in an international setting as participants came from some Asian countries. TMU as the organizer of this event and sponsored by the Ministry of Education (MoE) Taiwan, aimed to stimulate participant for:

1. Pursuing Ph.D. at IGPM Taipei Medical University;
2. Engaging in any collaboration in translational medicines;
3. Collaborating on the biomedical industry;
4. Participating in any TMU workshops and training programs.

All participants were enthusiastic and grateful for the workshop. They hope The Annual Biomedical Exploration Workshop will be held again in the upcoming years.

This event offered ≤ 25 travel grants for students, scholars, or professionals from Vietnam, Indonesia, and Malaysia who want to refine and enrich their knowledge and experimental skills in biomedical researches and applications. The travel grant from the committee included a free workshop fee, shared accommodation, and a travel award of NTD 5,000. I was also partially sponsored by INA-RESPOND for any expenses which were not covered by the grant.

I want to express my sincere gratitude to IGPM TMU, MoE Taiwan, INA-RESPOND, and NIH-NIAID for sponsoring my participation in The Annual Biomedical Exploration Workshop 2020. I would also like to acknowledge with special appreciation to my supervisor, dr. Dona Arlinda, for her permission and encouragement, which enable me to participate in training related to clinical research methodology. Thank you to Ms. Meity Siahaan, Ms. Kartika Chandra Budi Mulyono, and Ms. Yayu Nuzulurrahmah, who arranged the travel visa ticket. My thanks are also extended to Miss Hui-Yi Lin for her help in assisting and organizing the workshop to be on schedule and meeting the participants' needs. Special thanks to the Indonesian Student Association TMU for accompanying us during our stay in Taipei. Finally, I wish to thank all participants who had made this workshop so cheerful, memorable, and exciting.

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REPORT

# 5TH ANNUAL REPORT INTERNATIONAL MEETING

By: Aisyah Pratiwi

Tuberculosis (TB) is a global burden disease and one of the top ten causes of death worldwide; it is the leading cause of death from a single infectious agent. World Health Organization (WHO) estimated 10.0 million people suffered from TB in 2018. The number has been relatively stable in recent years, while Sustainable Development Goals (SDGs) target to end TB epidemic by 2030. It is also estimated that about one-quarter of the world's population has latent TB.

Reliable biomarkers that predict progression from latent to active TB and subsequent outcome to facilitate the development of better treatment and prevention is one of the most challenging tuberculosis research questions. Accommodating the need, Regional Prospective Observational Research in Tuberculosis (RePORT) consortium initiated by the National Institute of Allergy and Infectious Diseases (NIAID) as a collaborative research cross-national partnership reflects each national tuberculosis research goal while coordinating through common standards and practice. Six countries have taken part in the consortia, including Indonesia.

The 5th Annual RePORT International Meeting was held on 17-19 September 2019 in Manila, Philippines. The event was successfully organized by The Philippine Council for Health Research and Development (PCHRD) and the National Institute of Health-University of the Philippine. The theme, "New strategies for prevention of infection and progression to disease," was explored for the meeting. The activity aimed to conduct a forum for RePORT investigators to interact with select leaders in TB biomarkers, vaccine, drug, and diagnostic research. All delegates of RePORT consortia (RePORT India, RePORT Brazil, RePORT China, RePORT Indonesia, and RePORT Philippine) participated and updated research progress in the meeting. INA-RESPOND, as the RePORT Consortium Indonesia, commissioned three delegates (Retna Indah, Kanti Laras, and Aisyah Pratiwi) to participate in the forum. Retna Indah, the protocol specialist, was delegated to present RePORT Indonesia study current status. DR. Erlina Burhan, Protocol Investigator Indonesia, was also invited by the committee to deliver her experience in drug-resistant TB, short treatment regimen evaluation in Indonesia.

Dr. Padilla, the chancellor of the University of The Philippine Manila, gave a welcome speech saying that she was enthusiastic about the research partnership through the RePORT consortium. At the moment, the Philippines are facing half a million diagnosed active TB and has many complicated TB cases. She believed the gathering and interaction among researches, educators, and leaders would strengthen new strategies and approaches to solve TB challenges.

Dr.Dieffenbach, in his presentation, highlighted TB priorities and NIAID Updates. He agreed that no one country could solve TB problems alone, and only through collaboration could we transform TB research. With the advancement of new technologies such as ONIX

cellular technologies and deep sequencing, he hoped there would be a better way in understanding TB pathogenesis, such as in animal model and human response as well as the genomic level. It has also become a priority to understand how TB altered the immune system in HIV. Also, the PHOENIX project, one of the research funded by NIAID, was studying the potential of Delamanid and isoniazid as TB medication or prevention.

The forum invited various experts to present their studies' progress. Several TB vaccines were undergoing clinical trials. BCG-revaccination was evaluated for its efficacy in preventing TB in the adolescent. A new recombinant BCG vaccine, VPM1002, was assessed to prevent TB recurrence. Moreover, adjunctive immunotherapy onto multidrug regimens was suggested to play a critical role in reducing the global burden of TB. The priority population for immunization prevention based on each national needs also emerged into the discussion.

Talking about leveraging a cross-consortium observational cohort to advance the study of TB infection resistance, the speakers delivered enlightening TB scientific priorities. During this session, the recent headway of host genetics tuberculosis susceptibility, cytokine signatures predicting infection resistance, and host biomarkers were conferred. Another speaker brought up diabetes and immunological determinants of susceptibility to TB disease. He also presented the epidemiological evidence of infection resistant trough the index case of household contacts of DS-TB and MDR-TB. Moreover, a cross-consortia collaboration project's progress was also reported. One of the study co-joint between South Africa and Brazil, prospective profiling of eicosanoid and inflammatory balance in TB diabetes, had achieved preliminary results from the Brazilian site.

Before the closing remarks, young investigators from South Africa, China, India, and Indonesia had the opportunity to present their studies. They presented a poster from their selected abstract. All the experts and participants were engaged during the discussion. Dr. Aisyah Pratiwi, a Research Assistant at INA-RESPOND's site, Dr. Kariadi Hospital Semarang, represented Indonesia with her abstract entitled "Factors Related to Delayed Conversion in Intensive Phase Among DS-TB Patients in Indonesia.' During her activity as a research assistant, she was bothered about challenges on DR-TB treatment both from the patient's and health provider's perspective. She believed that the initial step to encounter TB and prevent DR-TB is managing DS-TB properly. Delayed sputum smear conversion is associated with unfavorable outcomes such as default, failure, mortality, and drug resistance. Thus, she underwent a study to determine the prevalence and risk factors of delayed conversion at the end of the intensive phase of DS TB patients in Indonesia. The study revealed that 17.1% of TB patients remain sputum smear-positive after two months of treatment. Sex, BMI, smoking, TB treatment history, DM status, cavity lesion, and initial bacillary were not determinant of persistent smear-positive. Transpired from panels discussion, it is better to develop the study into the scoring of the risk factor. Furthermore, it was a remarkable forum for young investigators to learn and interact with the expert.

At the end of the event, De La Salle Medical and Health Sciences Institute committee invited all the guests to visit the study site in Dasmarinas city, approximately one-hour-bus travel from Manilla. There they had one stop TB facilitates while the recruitment, treatment, specimen processing, and storage were in a well-organized building center. They also introduce the beauty of the Philippine while exploring Tagaytay Highland. Together with, it was very a warm welcome from Dr. Charles Yu, Project Investigators of De La Salle Institute, who arrange delicious dinner along with uplifting music.

We sincerely appreciate the RePORT Philiphine consortium for the superb organization of the meeting. Hopefully, the continuing consortium discussion would disseminate information and help address global TB Burden. Let's end TB!

INA-RESPOND Newsletter

FROM OUR LABORATOIRY

# RESPIRATORY SYNCYTIAL VIRUS: IN-DEPTH REVIEW (PART 1)

By: Yan Mardian

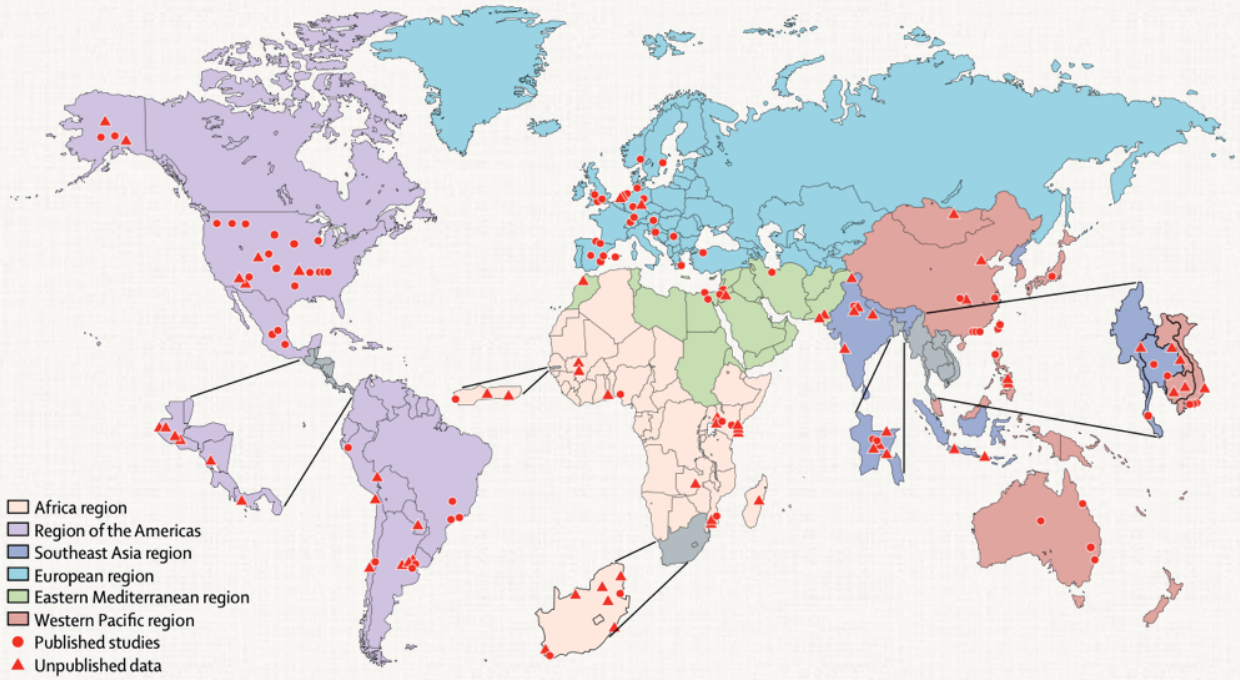


Fig 1. Location of studies reporting incidence, hospital admission, and in-hospital case fatality in children with RSV-LRTI

While the current whole world's attention is focused on the 2019 Novel Coronavirus (2019-nCoV), which causes lower respiratory tract infection (LRTI), the Respiratory syncytial virus (RSV); also causes LRTI, is a highly infectious and prevalent virus and much more widely distributed than 2019-nCoV. RSV was first isolated in 1956 from a laboratory chimpanzee with upper respiratory tract disease. RSV was quickly determined to be of human origin and was shown to be the leading worldwide viral agent of severe respiratory tract disease in children. Since its first isolation, extensive research has been conducted in epidemiology, diagnosis, and animal models for the infection, but there is no vaccine and only two approved antivirals available against the virus.[1]

RSV causes severe LRTI, especially in infants <6 months old and the elderly, posing public health concerns worldwide.[2] By the age of one year, 60–70% of children have been infected by RSV (2%–3% of whom are hospitalized), and almost all children have been infected by two years of age. This virus is estimated to cause approximately 33.8 million new episodes of acute lower respiratory infections annually in children aged <5 years worldwide, resulting in 3.2 million hospital admissions and 59,600 in-hospital deaths in children aged <5 years in 2015, which makes RSV as one of the leading causes of death of infants less than one year of age worldwide, second only to malaria. Also, early-life RSV infection is associated with the development of recurrent wheezing and asthma in infancy and childhood. [3,4]

RSV is ubiquitous, with relatively uniform distribution worldwide. In regard to weather conditions, the general rule in temperate climate regions, such as those of Europe or North America, is that RSV activity follows the decrease in temperature, which responsible for annual outbreaks during in the late fall, winter and early spring, while in cold climates it is nearly continuous throughout the year. Exceptions were observed in equatorial countries and tropical areas with high humidity, such as the Philippines and Mozambique, where viral circulation is seen primarily during the rainy season, although the residual activity is seen throughout the year. [3,5]

It was estimated that five countries (with about 43% of global under-5 children)—India, China, Nigeria, Pakistan, and Indonesia—contributed about half the global RSV-ALRI burden.

However, in Indonesia, despite its high burden, extensive and published research about RSV still lacks, as shown on the map below.[6] However, the preliminary data of the INA-RESPOND PEER-PePPeS Study and AFIRE Study showed the highest number of RSV amongst other all Respiratory viruses as the pathogen causing respiratory tract infection.

RSV manifestations range from coryza to severe lower respiratory tract infection (LRTI) including bronchiolitis and pneumonia, which can lead to hospitalization and respiratory failure. Here, we discuss the characteristics of RSV, focusing on the genetic and molecular aspects, their life cycle and pathogenesis-related to the infection, their impact on the clinical course of the disease as well as the current development of safe and effective preventive and therapeutic strategies for RSV.

**Characteristics of the Virus**

RSV (family Paramyxoviridae, order Mononegavirales) is an enveloped virus with a single-stranded negative-sense RNA genome of 15.2 kb. There are animal versions of RSV, including bovine RSV (BRSV) and pneumonia virus of mice (PVM), suggesting that species jumping occurred during the evolution of these viruses. However, there is no animal reservoir for human RSV.[1]

Structurally, the human respiratory syncytial virus is an enveloped, spherical virus with a diameter of approximately 150 nm. The RNA genome is packaged into the viral particle as a non-segmented negative-sense molecule, which encodes ten proteins: Internal structural proteins (matrix protein [M] and nucleoprotein [N]), proteins required for a functional polymerase complex (phosphoprotein [P] and polymerase [L]); Nonstructural proteins, which involved in evasion of the innate immune response (NS-1 and NS-2), externally exposed transmembrane glycoproteins (small hydrophobic protein [SH], glycoprotein [G], and fusion protein [F]); and Regulatory M2 proteins (M2-1 antitermination protein and M2-2, involved in transcription/replication regulation).[7]

The envelope of the virus is formed by four proteins associated with the lipid bilayer: the matrix (M) protein, the small hydrophobic (SH) protein, and the two glycosylated surface proteins: the fusion (F) and the attachment glycoprotein (G). F and G proteins are crucial for virus infectivity and pathogenesis since the G protein is responsible for the attachment of the virus to respiratory epithelial cells, while the F protein determines the entry of the virus, by fusing viral and cellular membranes, as well as the subsequent insertion of the viral RNA into the host cell inducing the formation of the characteristic syncytia. Moreover, the F and G proteins stimulate the neutralizing antibody immune response by the host.[5]

The RNA-dependent replication cycle of RSV is significant because it is error-prone and there is no proofreading mechanism. This allows for the rapid generation of single nucleotide polymorphisms (SNPs) and other mutations that allow for changes in virus virulence and avoidance of potential future antiviral agents or vaccines. The life cycle of RSV contains four sequential processes: attachment and fusion of the virion to the host cells, release the capsid contents to be transcripted into positive-sense antigenomes, replication of the genome by RSV polymerase-complex, and maturation of the progeny virus (assembly and budding) until it releases and ready to infect other host cells.[4,5]

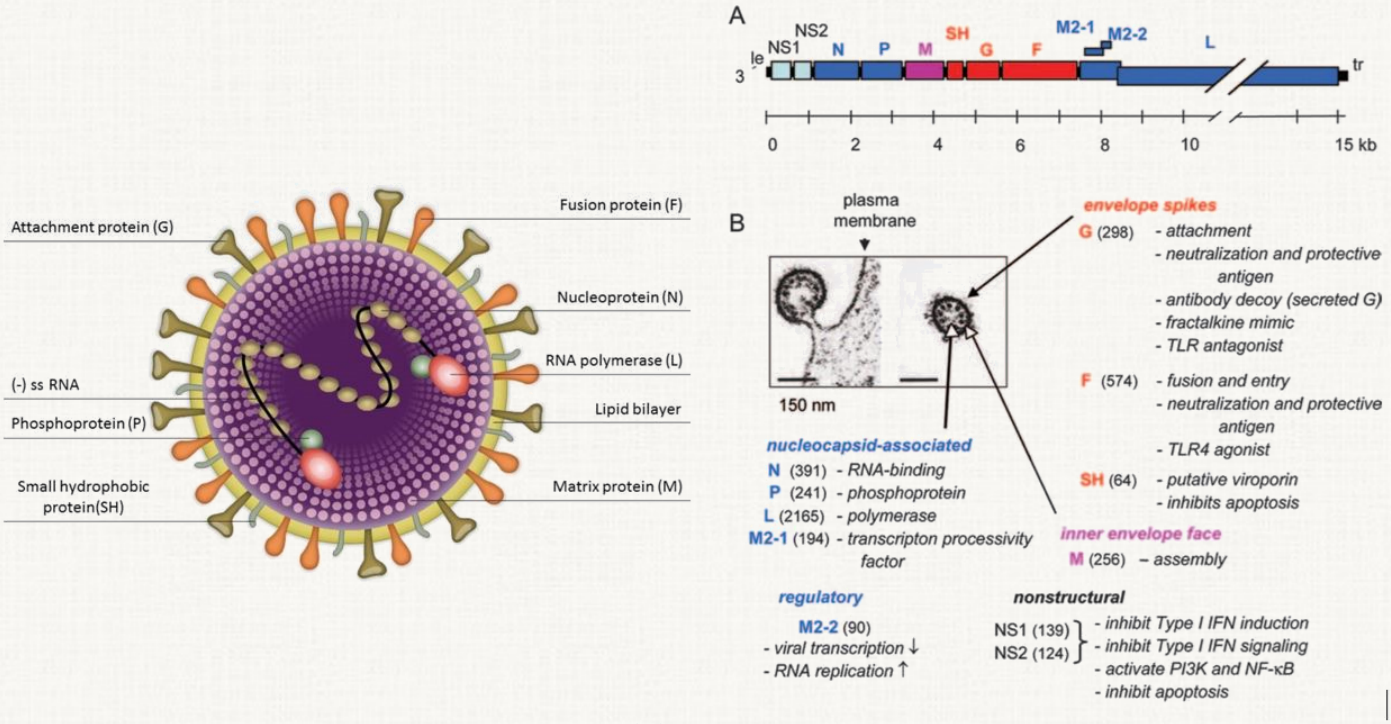


Fig 2. Structure of Respiratory syncytial virus (RSV); RSV virion, genome, and encodes protein

In 2011, Tayyari et al. reported on nucleolin as a receptor for RSV that binds to RSV-F. Expression of human nucleolin on insect cells that are not normally infectible by RSV made them susceptible to infection. Although nucleolin is a predominantly nucleolar protein, a small fraction can be found on the cell surface in vitro and in vivo. This cell surface nucleolin has been implicated as a receptor for a number of viral and bacterial pathogens along with various growth factors. Since nucleolin has been found on the surface in greater quantities on actively dividing cells, this may play a role in the preferential infection of the lower respiratory tract in young children because alveoli continue to grow until about two years of age, which is also when RSV infections decline significantly.[8]

The virus is classified into two subtypes: A and B, with about 50% genetic diversity in the G gene and 10% differences in the F gene. During epidemics, either Group A or B may predominate, or both Groups may circulate concurrently. Initially, 5 RSVA clades and 4 RSVB clades were identified, named GA1 to GA5 and GB1 to GB4, respectively. This list of clades has since grown to 16 RSVA clades and 22 RSVB clades. GA1, GA2, GA5, and GA7 as the current major circulating clades of RSVA worldwide, while The BA clade of RSVB predominates worldwide. In general, RSA A is more prevalent than B, and RSVA viral loads tend to be higher than RSVB viral loads by about a logarithm; the higher viral loads of RSVA in the nasopharynx may enable faster transmission between individuals. However, some studies report no significant correlation between clinical severity.[9]

**Pathogenesis**

Inoculation of the nose or eyes occurs by large particle aerosol or direct contact and results in viral replication in the nasopharynx, with an incubation period of 4 to 6 days, depending on host factors such as the age of the patient and whether it is the patient's primary infection with RSV. After inoculation into the nasopharyngeal or conjunctival mucosa, the virus rapidly spreads into the respiratory tract, where it targets its preferred growth medium: apical ciliated epithelial cells. There it binds to cellular receptors using the RSV-G glycoprotein, then uses the RSV-F fusion glycoprotein to fuse with host cell membranes and insert its nucleocapsid into the host cell to begin its intracellular replication. Host inflammatory immune response is triggered, including both humoral and cytotoxic T-cell activation, causing necrosis of respiratory epithelial cells, leading to downstream consequences of small airway obstruction and plugging by mucus, cellular debris, and DNA. The resulting clinical findings are the hallmarks of bronchiolitis: increased airway resistance, air trapping, and wheezing. Pneumonia accounts for the hypoxia frequently detected in RSV-infected infants. Infection normally is highly restricted to the superficial cells of the respiratory epithelium. Ciliated cells of the small bronchioles and type 1 pneumocytes in the alveoli are major targets of infection in the lower airway. It is likely that other cells, including nonciliated epithelium and intraepithelial dendritic cells (DCs), are also infected, but the basal cells appear to be spared.[7]

Viral transmission occurs by direct inoculation of contagious secretions from the hands or by large-particle aerosols into the eyes and nose, but rarely the mouth. The modes of nosocomial spread of RSV were examined by comparing rates of infection in hospital staff who had cuddled infected infants, those who had touched only contaminated toys and subsequently touched their

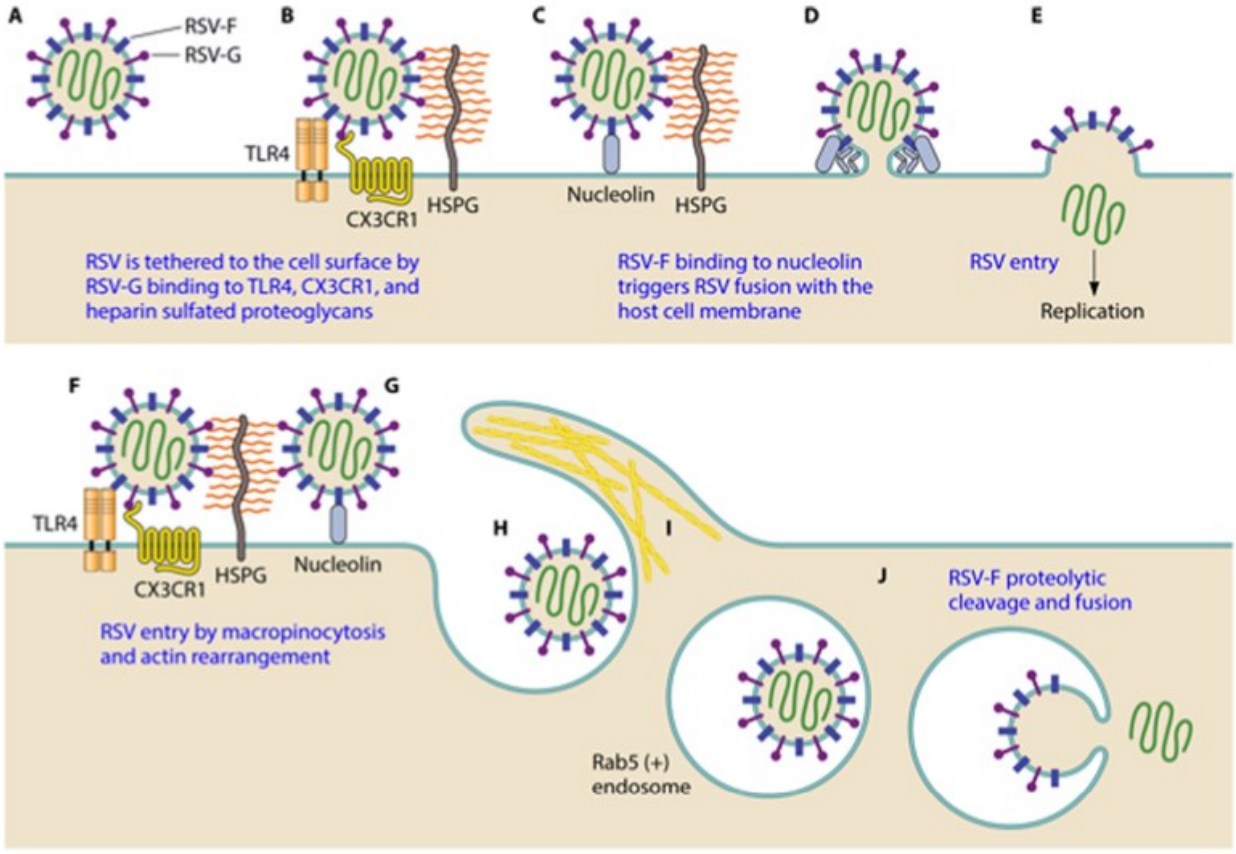


Fig 3. Binding and and entry of RSV into host cells trough cell surface nucloelin.

own eyes or noses, and those who had sat close to but no more than about 1 m (3 ft) away from infected infants. Those who had cuddled infants or touched toys became infected, but those who had only sat near the infants did not. This result suggests that transmission requires close or direct contact with large droplets or fomites. The prolonged survival of RSV on the skin, cloth, and other objects emphasizes the importance of fomites in the nosocomial spread and of handwashing in controlling the infection.[7]

RSV causes a neutrophil-intensive inflammation of the airway during both upper and lower respiratory tract infections in infants. Infection can be accompanied by eosinophilia that is particularly marked in the most severe cases of RSV LRTI. RSV is relatively less cytopathic than other respiratory viruses. It is therefore thought that the majority of damage done to the airway during RSV infection is mediated by the immune response and not by viral replication itself. Although RSV does not cause significant cytopathic effect in vitro, it causes significant pathology in the airway in vivo. In adults, RSV replication continues in the airway for about 8 days (6 days longer than the influenza virus). In a study that looked at RSV infection in a hamster model, 3 days after infection, there was significant rounding of RSV-infected columnar ciliated cells in the airway. These RSV-infected columnar cells eventually sloughed into the lower airway bronchioles, causing an obstruction.[4]

In addition to lower airway obstruction, infant hospitalizations due to RSV are associated with chronic wheeze and asthma in children. The complexity of the immune response and its change during development provide a link between wheeze, asthma, and RSV infection. This association may involve a key cytokine called IL-33. There is a large body of support for IL-13 as an independent and "pivotal" cytokine in the genesis of asthma. RSV induced the expression of IL-33 in the lungs of neonates. The increase in IL-33 production during RSV infection resulted in an increase in group 2 innate lymphoid cells and their production of IL-13 (189). IL-33 binds the IL-33 receptor ST2 on nuocytes (naïve CD4+ T cells), triggering the production of IL-4, IL-5, and IL-13, cytokines that are implicated in asthma genesis.[4]

Airways that have been damaged by viral infections are susceptible to secondary bacterial infections. In a series of studies examining patients admitted to hospitals with RSV infections, between 17.5 and 44% of patients also tested positive for a lower respiratory tract bacterial coinfection, with Streptococcus pneumoniae (Gram-positive) and Haemophilus influenzae (Gram-negative) being the most common bacterial isolates. Compared to RSV infection alone, a bacterial coinfection combined with RSV infection correlates with more severe disease. In addition to bacterial coinfection, the degree of nasopharyngeal colonization by Gram-negative or potentially pathogenic bacteria correlates with inflammatory cytokine levels and disease severity during RSV infection.[4]

Instead, preexisting and sustained colonization by potentially pathogenic bacteria may make the host more susceptible to subsequent RSV infection. It has been shown in vitro or in vivo (using the cotton rat model) that treatment with S. pneumoniae prior to RSV challenge results in enhanced RSV replication. RSV infection increases bacterial binding by causing infected cells to upregulate cell surface expression of a number of bacterial receptors, including intercellular adhesion molecule 1 (ICAM-1), platelet-activating factor receptor (PAF-r), and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), and bacterial binding to RSV-G glycoprotein expressed on the surface of infected cells or on viral particles. The increased bacterial binding and ciliary dyskinesia together have been postulated as a mechanism for longer bacterial persistence in the lower respiratory tract during RSV infection and may explain the high likelihood of bacterial coinfection. In summary, a positive feedback loop may exist wherein RSV infection enhances bacterial colonization of the lower respiratory tract, which in turn increases RSV replication.[4]

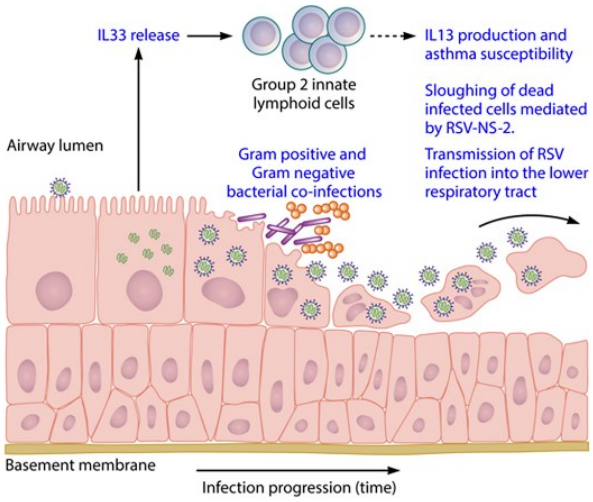


Fig 4. Pathology of RSV in the airway.

(to be continued..)

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INA-RESPOND Newsletter

# EXERCISE FOR THE ELDERLY: KEEP MOVING FOR LIFE

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LIFESTYLE & SPORT

**Introduction**

Aging is a process of inherent change that has separate or joint effects on individual identity. Aging brings about physiological, psychological, and other kinds of changes to the human body. It is important that although some of the changes brought by aging can't be controlled, some can be controlled feasible in many of the body organs through exercise.[1]

Exercise and physical activity are good for just about everyone, including elderly or older adults. Because activity levels generally decline with advancing age, the number of inactive older adults will most likely increase dramatically. As the population of older adults increases, it will become important to advise sedentary patients to become more physically active. Regular exercise in older adults provides many health benefits, including improvement in blood pressure, blood sugar, lipid profile, osteoarthritis, osteoporosis, and neurocognitive functions. Regular physical activity is also associated with decreased mortality and age-related morbidity in older adults.[2]

**Prescribing Exercise for Elderly**

Exercise programs for the elderly consist of four major components: endurance, strength, flexibility, and balance.

1. Endurance (aerobic exercise)

Older adults develop poor endurance as a result of many factors. Aging itself is associated with declining skeletal muscle mass and capillary blood flow, inadequate nutritional intake, and impaired oxygen uptake. In addition to these factors, several common disease processes in elderly patients are shown to affect endurance. Approximately 11% of patients older than 70 years old may have chronic obstructive pulmonary disease, which further decreases oxygen exchange in the lungs. In addition to being a common cause of poor endurance, cardiovascular disease is the second most common disease and the leading cause of death in older people.

For patients at risk for cardiovascular diseases, such as those who have hypertension and elevated lipid profiles, aerobic exercise has been associated with average decreases of 11 mmHg in systolic blood pressure and 8 mmHg in diastolic. For patients who have diabetes, aerobic exercise can have beneficial effects. Studies have shown improvements in insulin sensitivity as measured by glucose uptake after aerobic exercise training, both in experimental animals. and in humans. Diabetic patients also show improved lipid profiles, blood pressure, and energy expenditure with aerobic exercise programs. [3]

Exercise prescription: For a deconditioned older adult, low-intensity exercise may be the safest place to start. The goal should be to able to maintain the heart rate between 60% to 70% of the heart rate maximum (220-age). Aerobic exercise such as treadmill or street walking, bicycling, swimming are appropriate. These may be started twice weekly for 20-30

minutes and increased to approximately 150 minutes per week.3

2. Strength (resistance training)

Muscle strength declines by 15 percent per decade after age 50 and 30 percent per decade after 70. This decline is principally the result of sarcopenia (loss of muscle mass) and occurs to a higher degree in older women than men. Strength is intrinsic to daily function, especially in the elderly. Most of the variance in walking speed in the elderly is related to leg strength, and increased strength has been shown to improve walking endurance.[2]

Exercise prescription: For severe deconditioned elderly and those who have established cardiac risks, low-intensity programs may be prescribed as little as twice weekly, with the use of only body weight as resistance. Patients should perform 10-15 repetitions per set in each of the major upper and lower extremity muscle groups and three sets per session for each muscle group. Frequency should then be increased to three times weekly and then light resistance such as dumbbell or wrist weights may be added.[3]

3. Flexibility

Flexibility is the Range of Motion (ROM) around a joint and is associated with injury prevention through all life stages. The aging process results in decreased collagen synthesis in skin, ligaments, tendons, and underlying tissues, which may lead to slower healing and adaptation to changing movement patterns.[3] Adequate flexibility can reduce chronic low back pain, maintain the ability to perform daily activities and prevent falls.[4]

Exercise prescription: There are no definite precautions against or contraindications to flexibility exercise. Stretching should ideally be performed daily. A general prescription recommended for other age groups is four to five repetitions of approximately 30 seconds each for the most important joints and muscle groups. Flexibility exercise is low intensity and can be performed sitting or lying down. It may be an especially useful warm-up for patients with impairments in endurance and balance.[3]

4. Balance

Deterioration in one or more aspects of the postural control system may occur naturally with age. Consequently, falls are the leading cause of accidental death in older persons.

Tai Chi is a form of exercise training that shows positive effects in balance. One study suggests that Tai Chi participants were 27% less likely to fall than the control group, and other studies have shown improvement in fall risk assessment scores.

Balance exercise may easily be incorporated into strength or endurance routines three or four times weekly. The American College of Sports Medicine recommends that a balanced exercise program includes both static and dynamic balance components. The former includes a wide-base stance, narrow-base stance, and single-leg stance held for 30 or more seconds with eyes closed. The latter generally consists of walking exercises with various bases of support, beginning with a normal gait and progressively narrowing the base to heel-to-toe gait. For both of these components, the intensity may be varied by initially using aids such as a raised bar or countertop, then withdrawing the aids. Although adults who have disabilities resulting from stroke, multiple sclerosis, neurotrauma, or amputation may require assistance and supervision from others when starting balance exercise, the prescribing practitioner should bear in mind the special importance for these patients to achieve independence in this modality.[3]

**Contraindications for participating in exercise**

There are some contraindications for older adults to participate in an exercise program, such as:[3]

- Unstable angina or severe left main coronary disease
- End-stage congestive heart failure
- Severe valvular heart disease
- Malignant or unstable arrhythmias
- Elevating resting blood pressure (ie, systolic >200 mmHg, diastolic >100 mmHg)
- Large or expanding aortic aneurysm
- Known cerebral aneurysm or recent intracranial bleed
- Uncontrolled or end-stage systemic disease
- Acute retinal hemorrhage or recent ophthalmologic surgery
- Acute or unstable musculoskeletal injury
- Severe dementia or behavioral disturbance

**Conclusion**

Regular exercise is the most effective "treatment" available to prevent and treat a wide range of diseases, and maintain physical fitness, muscular strength and activity in old age (especially quality of life). Despite the known facts of the benefits of physical activity, more than 90% of older people fail to take enough regular exercise to improve their health. We need political action to achieve public awareness of these facts and encourage older people to increase their exercising habits. The exercise recommendations should be individually tailored to the abilities, precautions, and goals of each person. It is recommended to have a consultation with the sports medicine doctor for the older adults before participating in an exercise program.

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# INA-RESPOND Newsletter

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